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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,420	11/21/2001	Junichi Mineno	1422-0506P	9784

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,420	MINENO ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 29, 2004 has been entered.

Preliminary Remark

Applicants are advised that the Examiner of record has been changed to Young J. Kim. All further correspondences should be directed to the above examiner of record.

Claims 7-21 are pending and are under prosecution.

Claim Objections

Claims 10 and 11 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 10 recites the limitation, "wherein said mixture of fragmented DNAs is a mixture of DNAs having distribution ratio of 1 to 5 as defined by the size ratio (distribution ratio) of the maximum size of fragmented DNA to the minimum size of fragmented DNA." Claim 10 depends from claim 7, which already recites this limitation.

Therefore, claim 10 does not further limit its parent claim 7.

Claim 11 recites the limitation, "wherein said mixture of fragmented DNAs is a mixture of DNAs having a size convergence rate of 80% or more." Claim 11 depends from claim 7, which recites that the mixture of fragmented DNAs having, "a size convergence rage of 80% or more" is generated.

Therefore, claim 11 does not further limit its parent claim 7.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 further limits its parent claim 7 by recitation of the below steps:

(a) subjecting a genomic DNA to said DNA fragmentation means;

(b) ligating adapter DNA to the fragmented DNAs obtained in step (a), thereby giving DNA fragments; and

(c) carrying out nucleic acid amplification using the DNA fragments obtained in step (b) as a template and amplification primers, to give a genomic DNA library.

While claim 13 makes sense to its dependency on claim 7 for the fragmentation means, claim 13 becomes indefinite in the recitation of steps (b) and (c) as the parent claim 7 is drawn to a method that fragments a genomic DNA and amplifies the fragmented DNAs. Therefore, it becomes indefinite when the ligation is to occur and whether the amplification of claim 7 is to

occur or the amplification of step (c) in claim 13 is to take place said amplification of claim 7, causing confusion as to how the steps (a)-(c) are to occur in conjunction with steps (1)-(2) of claim 7.

For the purpose of prosecution, it is assumed that claim 13 conducts the fragmentation method of claim 7, step (1), and conduction ligation step of claim 13(b); followed by the amplification of claim 13(c).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a genomic DNA library, said method involving a hydrodynamic point-sink shearing fragmentation method, does not reasonably provide enablement for a method for producing a genomic DNA library, said method involving ***any*** fragmentation means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the

invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

(B) Amount of direction or guidance presented:

Looking at the instant specification, Applicants discuss ***a single type*** of fragmentation method that would produce the claimed distribution ratio and size convergence:

> "More concretely, the physical method includes the hydrodynamic point-sink shearing method...In the method for producing a genomic DNA library of the present invention, the ***hydrodynamic point-sink shearing*** method is preferred from the viewpoint of efficiently obtaining a fragmented DNA which ***meets the requirements*** for the distribution ratio, the size convergence rate, and the average size" (page 16, lines 5-12).

> "Each of genomic DNA for the gastric cancer cell line MKN74 and genomic DNA for the esophageal squamous cell cancer cell line TE6 was extracted by a commonly used nucleic acid extraction method...The resulting DNA solution was fragmented (sheering speed: 5) by using random DNA fragmentation apparatus ***Hydroshear™***..." (page 27, lines 8-16)

While Applicants make a prophetic statement regarding other types of fragmentation methods embraced by the instant application, which would produce the desired distribution ratio, the size convergence rate, and the average size, not a single type fragmentation method other than hydrodynamic point-sink shearing method is disclosed.

> "Incidentally, there are also encompassed in the scope of the present invention applications of other methods ***having functional abilities to give a fragmented DNA which meets the requirements for the distribution ratio, the size convergence rate, and the average size, in place of the physical method in the method for producing a genomic DNA library of the present invention***." (page 16, lines 21-25)

(C) Absence of Working example:

Looking at the instant specification, Applicants discuss ***a single type*** of fragmentation method that would produce the claimed distribution ratio and size convergence:

> "Each of genomic DNA for the gastric cancer cell line MKN74 and genomic DNA for the esophageal squamous cell cancer cell line TE6 was extracted by a commonly used nucleic acid extraction method...The resulting DNA solution was fragmented (sheering speed: 5) by using random DNA fragmentation apparatus ***Hydroshear™***..." (page 27, lines 8-16)

(D) Nature of the invention:

The nature of the invention relates to a method of generating a DNA library, said method producing DNA fragments of requisite distribution ratio of 1 to 5, having a size convergence rate of 80% or more.

(E) State of Prior art: Lucito et al. disclose a method of generating a DNA library involving restriction enzymes (page 4487, 2nd column, 2nd paragraph).

(F) Skill level: The skill level of the artisan in question is considered high.

(G) Unpredictability of the art: It remains unpredictable what other fragmentation method would necessarily produce the DNA fragments having the claimed distribution ratio as well as the size convergence rate of 80% or more.

(H) Breadth of the claims: The breadth of the claims embrace a method of producing a DNA library having a plurality of DNA fragments having the claimed distribution ratio and size convergence, wherein the method of producing such fragments is ***any*** fragmentation means.

MPEP 2164.01, in discussing the test of enablement, states:

> "Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of ***whether that disclosure, when filed***, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to ***make and use*** the claimed invention."

One of skill in the art, in order to practice the method fully commensurate in scope of the claims, would look to the specification in order to practice the method of producing a DNA library involving ***any*** fragmentation means, said fragmentation means producing a particular distribution ratio and size convergence, but would only find guidance pertaining to a single method of fragmentation – hydrodynamic point-sink shearing. One of skill in the art then would look to the prior art in order to determine what fragmentation methods would necessarily produce the DNA fragments of the requisite characteristics to which none would be found, requiring undue experimentation of said one of skill in the art to practice the invention fully commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Oefener et al. (Nucleic Acids Reearch, 1996, vol. 24, no. 20, pages 3879-3886).

Oefener et al. disclose a method of producing a plurality of random DNA fragments via point-sink fragmentation method, which is hydrodynamic (or physical means) in mechanism (page 3880, 1st column, 2nd paragraph).

Oefener et al., after producing the plurality of randomly sheared DNA fragments, are cloned via subjecting the sheared DNA fragments to blunt-end ligation into a unique *Eco*RV site

within tet^r gene of pBR322, (page 3880, 2nd column, 2nd paragraph) resulting in the "amplification" (amplification is read broadly so as to include any method that results in the increase of the DNA fragments) of said DNA fragments.

Oefener et al. disclose that the major advantage of their method produces greater randomness of fragmentation sites and >90% yield fragments over 2-fold size range (page 3876, 2nd column, 2nd paragraph).

While Oefener et al. do not explicitly disclose that the DNA fragments produced by their method has the distribution ratio of 1 to 5 and a size convergence rate of 80% or more, the instant specification explicitly evidences that such method would necessarily produce the DNA fragments of the above-recited characteristics:

> "More concretely, the physical method includes the hydrodynamic point-sink shearing method...In the method for producing a genomic DNA library of the present invention, the ***hydrodynamic point-sink shearing*** method is preferred from the viewpoint of efficiently obtaining a fragmented DNA which ***meets the requirements*** for the distribution ratio, the size convergence rate, and the average size" (page 16, lines 5-12).

The fragmentation method is disclosed as being "point-sink" (page 3881, 2nd column, bottom paragraph).

The fragmentation (or shearing) method employed by Oefener et al. is disclosed as producing fragments ranging from 296 bps to 12 kbps.

Therefore, Oefener et al. anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oefener et al. (Nucleic Acids Reearch, 1996, vol. 24, no. 20, pages 3879-3886) in view of Lucito et al. (PNAS, 1998, vol. 95, pages 4487-4492).

Preliminarily, claim 7-12 are included in the 103(a) rejection based on an alternative (narrower) interpretation of the term, "amplification," as that which employs at least a primer and a polymerase (i.e., PCR), resulting in an increase of the template nucleic acid molecules.

Oefener et al. disclose a method of producing a plurality of random DNA fragments via point-sink fragmentation method, which is hydrodynamic (or physical means) in mechanism (page 3880, 1st column, 2nd paragraph).

Oefener et al. disclose that the major advantage of their method produces greater randomness of fragmentation sites and >90% yield fragments over 2-fold size range (page 3876, 2nd column, 2nd paragraph).

While Oefener et al. do not explicitly disclose that the DNA fragments produced by their method has the distribution ratio of 1 to 5 and a size convergence rate of 80% or more, the instant specification explicitly evidences that such method would necessarily produce the DNA fragments of the above-recited characteristics:

> "More concretely, the physical method includes the hydrodynamic point-sink shearing method...In the method for producing a genomic DNA library of the present invention, the ***hydrodynamic point-sink shearing*** method is preferred from the viewpoint of efficiently obtaining a fragmented DNA which ***meets the requirements*** for the distribution ratio, the size convergence rate, and the average size" (page 16, lines 5-12).

The fragmentation method is disclosed as being "point-sink" (page 3881, 2nd column, bottom paragraph).

The fragmentation (or shearing) method employed by Oefener et al. is disclosed as producing fragments ranging from 296 bps to 12 kbps.

Oefener et al. do not employ ligation of adapters to their fragmented DNAs followed by an amplification of said adapter ligated DNA fragments via use of primers.

Oefener et al. do not employ PCR method for amplification of the adapter ligated DNA fragments.

Oefener et al. do not employ primers that comprises a sequence complementary to the adapters of the adapter ligated DNA fragments.

Lucito et al. disclose a method of generating a genomic DNA library involving the steps of fragmenting a genomic DNA; ligation of adapters thereto, producing adapter-ligated DNA fragments; followed by the PCR amplification said adapter-ligated DNA fragments (page 4487, 2nd column, 2nd paragraph). The amplification is achieved via use of AmpliTaq, in a thermocylcing reaction, said reaction involving temperatures of 77 and 95°C (page 4487, 2nd column 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Oefener et al. with the teachings of Lucito et al. for the following reasons.

Oefener et al. clearly and explicitly discuss that their method involving random fragmetion of genomic DNA molecules via point-sink flow system is for generating DNA library (page 3876, 1st column, *Introduction*) and subcloning prior to DNA sequence analysis.

While Oefener et al. employ shotgun cloning method in amplifying their fragmented DNA molecules, one of ordinary skill in the art would have been easily motivated to modify the teachings of Oefener et al. with the well-known amplification techniques such as adapter-mediated amplification of Lucito et al., because by doing so, one ordinary skill in the art would have been able amplify DNA fragments for DNA sequence analysis, such as nucleic acid sequencing, AFLP, etc.

One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success at combining the teachings as Oefener et al. already employ the adapter ligation to the DNA fragments. While the artisans employ the adapters for introducing the adapter-ligated DNA fragments into the vector, one of ordinary skill in the art would have had a reasonable expectation of success at employing primers which were complementary to these adapters for the amplification of the fragments as evidenced Lucito et al.

With regard to the limitation of DNA library maintaining 85% or more copy numbers of a set of genes or sequences on a genomic DNA, since Oefener et al. employ an identical method of fragmenting DNA molecules and as Lucito et al. employ an identical method of adapter-assisted amplification, barring evidence to the contrary, the combination of the method would necessarily produce a DNA library maintaining 85% or more copy numbers of a set of genes.

According to *In re Best* 195 USPQ 430, 1997, the court stated that, "Patent Office can require applicant to prove that prior art products do not necessarily or inherently posses characteristics of his claimed product wherein claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes; burden of proof is on applicant" (pp. 430).

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oefener et al. (Nucleic Acids Reearch, 1996, vol. 24, no. 20, pages 3879-3886) in view of Lucito et al. (PNAS, 1998, vol. 95, pages 4487-4492) as applied to claims 7-16 above, and further in view of Sorge et al. (U.S. Patent No. 5,556,772, issued September 17, 1996) .

The teachings of Oefener et al. and Lucito et al. have already been discussed above.

Particularly, Lucito et al. employ a thermostable DNA polymerase, AmpliTaq DNA polymerase in their amplification method (page 4487, 2nd column 2nd paragraph).

Oefener et al. and Lucito et al. do not employ a DNA polymerase having a proofreading activity for the amplification.

Oefener et al. and Lucito et al. do not employ a combination of a DNA polymerases having a 3'→5' exonuclease activity and a DNA polymerase lacking 3'→5' exonuclease activity.

Oefener et al. and Lucito et al. do not employ a combination of α type DNA polymerase and non-α, non-pol I type DNA polymerase.

Sorge et al. disclose a method of amplifying a nucleic acid with a combination of proofreading DNA polymerase (*Pfu*) and *Taq* DNA polymerase (column 2, lines 7-13).

Pfu DNA polymerase is disclosed as having 3'→5' exonuclease activity (column 3, lines 5-46), while *Taq* Dna polymerase is discloses lacking 3'→5' exonuclease activity (column 4, lines 14). It is well-known that 3'→5' exonuclease activity is synonymous with "proofreading" activity (column 6, line 6).

The instant specification evidences that *Pfu* DNA polymerase is an α type DNA polymerase [0117].

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings with Oefener et al. and Lucito et al. with the teachings of Sorge et al., because by doing so, one of ordinary skill in the art at the time the invention was made would have been able to amplify the desired nucleic acid with "superior synthesis results" via use of a combination of the DNA polymerase of Sorge et al. rather than the use of a single DNA polymerase which had been employed by Oefener et al. and Lucito et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained

by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
3/19/05

YOUNG J. KIM
PATENT EXAMINER

yjk